



Ge-68/Ga-68 Generators- FDA Perspective

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Outline

- Brief discussion of the Ge/Ga-generator, characteristics and elution process
- Generator DMF
- SS peptide based radiopharmaceutical kit
- Issues of the generator eluate and Ga-chelation reactions

Introduction

Ge-68/Ga-68 generators have recently attracted interest as they:

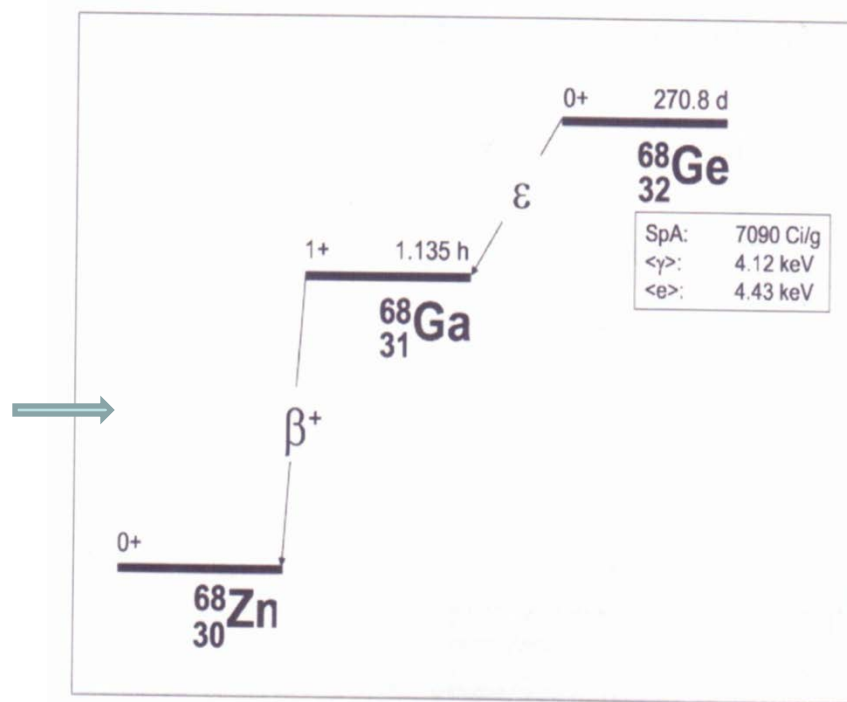
- Allow for simple and fast preparation of Ga-68-radiopharmaceuticals for PET imaging
- Ga-68-labeled peptides have shown promise for imaging NETs

Some Favorable Properties of Ga-68

- Ga-68 has a short half-life (68 minutes)
- Forms stable complexes with various ligands
- No need for on-site cyclotron
- Abundant positron emission

What is the Ge/Ga-Generator?

- Consists of a short glass column packed with a solid support
- Ge-68 is absorbed onto the solid matrix
- Ge-68 (parent) decays to Ga-68 (daughter) decays to Zn-68 (stable)
- The Ga-68 is washed off the column with an appropriate solution



Production of Ge-68 raw material

- Ge-68 is produced in an accelerator using variety of nuclear reactions and target materials

–E.g. $^{\text{nat}}\text{Ga} (p, xn) ^{68}\text{Ge}$

(Target materials and targetry is beyond the scope of this presentation)

Separation of Ge-68

- Ge-68 is isolated from the irradiated target as chloride salt by:
 - Extraction
 - Ion exchange
 - Volatilization
 - Precipitation
- The Ge-68 chloride solution is used to load the Ge/Ga-generator

Elution of the Ge/Ga-Generator

- Several solutions have been used for generator elution:
 - EDTA and Oxalate
 - HCl (aqueous)
 - Followed by direct reaction with a precursor
 - Processing (Anionic/Cationic cartridges)

Trace Metals in the Generator eluate

- Trace metals in the generator eluate, such as Zn, Fe, Cu may compete for the ligand, and affect performance during the Ga-68-radiopharmaceutical preparation.

Regulatory Pathway for Ge/Ga Generator

In contrast to the Mo-99/Tc-99m generator, the Ge/Ga generator has no current stand alone clinical indication, and therefore cannot be submitted as a NDA. A drug master file (DMF Type II) is currently the preferred pathway

(DMFs are not approved or disapproved by the FDA, rather they are reviewed for adequacy/acceptance in relation to a submitted application using the indicated generator)

DMFs

- Because DMFs contain proprietary information, a letter of authorization (LOA) from the DMF holder of the referenced DMF is needed.
- The LOA permits FDA to access the DMF

Some Information needed in a Ge-68/Ga-68 Generator DMF

- Source of the Ge-68
- Target composition and irradiation parameters
- Production method (Cyclotron, etc.)
- Isolation/separation method for Ge-68
- Column and generator preparation
- Quality control (Ge-68 and Ga-68 eluate)
-(21 CFR 314.420)-

Ga-68-Radiopharmaceutical INDs

- Currently FDA is making Ga-68-radiopharmaceuticals available through IND studies.
- The quality of the Ga-68-radiopharmaceutical is assured by CMC review.

Ga-68-Radiopharmaceuticals: kit formulation

- The FDA encourages that the Ga-68-radiopharmaceutical and the kit formulation from which it is prepared should be submitted under a single NDA
- The kit should be compatible with one or more commercial generators.

Generators and Labeling Issues (1)

Generator solid supports differ and therefore elution characteristics may differ

- HCl concentration and volume used for elution vary
- Generator eluate processing:- no processing, fractionation, acetone/HCl, ethanol/HCl, cationic or anionic exchanger cartridges
- Reaction conditions are not adequately controlled:- temperature, reaction times for the same peptide precursor differ

Generators and labeling issues (2)

- Control of the eluate composition prior to labeling of medically useful radiotracers may make the labeling conditions independent from the generator used

FDA working to ensure:-

- Ge/Ga-generator availability
- Adequate purity and quality of the Ge/Ga generator eluate
- Radiopharmaceutical kit performance

Conclusion

- The Agency will continue to work with the regulated industry moving forward to:
 - facilitate the availability of Ge/Ga-generators (DMFs)
 - encourage the development of kit formulation for Ga-68 radiopharmaceuticals (NDAs)
 - communicate with the Agency



THANK YOU